http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v8i10.06

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

A Rare Case of Primary Haemochromatosis in India

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Abstract
Haemochromatosis is a genetic disease associated with progressive systemic iron overload causing multi system injury. This has been widely reported among the people of Northern European origin with the common mutations being C282Y and H63D. However, this is rare and under reported in the Asian subcontinent. We report a reformed alcoholic patient with worsening liver disease having Haemochromatosis, negative for common mutations despite abstinence
Keywords: *Alcohol; Haemochromatosis; Liver disease.*

Introduction

Trousseau described the first case of Hereditary Haemochromatosis (HH) in 1865.[1] HH is a Genetic disease resulting in systemic iron overload causing multi organ dysfunction. The most common organs involved are the liver, pancreas, gonads, heart and brain. If it is not detected early it can cause devastating injury to the respective organs. Primary Haemochromatosis is rarely detected in the developing countries. The most common gene associated is HFE (C282Y, H63D) gene mutation seen in the Northern European countries. We report a Non- HFE gene Primary Haemochromatosis.

Case Report

A 49-year-old Gentleman, presented to the clinic with history of fatigue and jaundice for 2 years, bilateral pedal oedema, bilateral knee and ankle arthralgia for the past 6 months duration. He reported consumption of approximately 60 units of alcohol every week for 15 years and has been abstinent for past two years. He was also a reformed smoker for the past couple of years (10 pack years). On further questioning he revealed that he had decreased libido and erectile dysfunction of four years duration and generalised hyper pigmentation for the past 6 months. He has been taking medication intermittently for the above-mentioned problems from various general practitioners but did not find any relief.

He does not have any significant past history apart from his smoking and Alcohol habits which he stopped two years back. There was no history of Diabetes or Hypertension. He is married and has two girls aged 8 and 10 years with no similar complaints in the family or siblings. There was no past history of repeated blood transfusion or blood borne viral infections.

On examination he was moderately built with BMI of 23kg/m^2. He had icterus and bilateral pedal oedema, madarosis with generalised hyper pigmentation. There was sparse axillary, pubic and facial hair and his testicular volume was 20ml bilaterally which was soft inconsistency.

Patient was provisionally diagnosed as chronic liver disease secondary to alcohol and was treated with diuretics, beta-blockers and advised review for further evaluation in view of hyper pigmentation and hypogonadism. However, he defaulted and came to emergency department with hepatic encephalopathy. Due to generalised hyper pigmentation and deranged liver function tests, hemochromatosis was considered. Ferritin and transferring saturation was elevated and subsequently liver biopsy was done which showed loss of architecture with thick fibrosis inflamed bands with nodular hepatocyte clusters with vacuolated cytoplasm, and brownish pigments. Focal ductal proliferation and focal cholestasis seen. Pearls stain- intracytoplasmic iron pigments in hepatocellular nodules (3+to 4+), features suggestive of cirrhosis of liver with increased iron. HFE gene mutationanalysis for hemochromatosis (C282Y, H63D) were negative. However, the other mutations Ferroportin gene, hepcidin, Transferrin receptor 2 (TFR-2) mutation was not sent due to financial constraints.

Patient was started on oral Prednisolone 5mg, Thyroxine 50 mcg, Methylcobalamine1500mcg, Folic acid 5mg, spironolactone 25 mg, frusemide 40mg, lactulose to maintain 2-3episodes of bowel movements per day and Propranolol 20 mg twice a day, Injection testosterone 250 mg was started in a lower dose and advice to repeat after 4 weeks. Dietaryadvice was given in order to reduce foods rich in iron. Phlebotomy was started on a weekly basis and approximately 300 ml whole blood was removed and planned weekly phlebotomy up to 1-2 year or until ferritin reduces to below 50. Defasirox was planned to be started if patient does not tolerate phlebotomy in future.

Differential Diagnosis

Based on past history of significant alcohol intake, chronic liver disease was initially attributed to alcohol. However due to elevated alkaline phosphatase infiltrative disorders were considered. Computer Tomography was done which showed only chronic liver disease with peri-portal, pancreatic, retro peritoneal collaterals. There was also indirect hyperbilirubinemia hence direct coombs test was done to rule out autoimmune haemolyticanaemia, and vitamin B12 supplementations were started along with folic acid since blood picture showed macrocytic blood picture though serum levels were more than 2000 pg. /ml,and patient gave history of taking multivitamin injection at a nearby clinic. Lipid profile was done to rule out dyslipidaemia which might cause Non-alcoholic steatohepatitis. Alcohol related iron overload was considered; however, the patient has been abstinent for 2 years, and iron levels tend to reduce within 2-6 weeks of abstinence.

Clinical Diagnosis

Chronic Liver disease with portal hypertension, with grade I Oesophageal Varices with (Partial Pan-hypopituitarism) secondary Hypocortisolism, Central Hypogonadism and hypothyroidism, due to Hereditary Hemochromatosis; Diabetes mellitus

Table 1: Investigations

	March 2016	December 2016	January 2017
Haemoglobin (g/dl)	**12.9**	**12.2**	**12.9**
Total count(x10^3/mm^3)	7.2	14.3	
Differential Count (%)	N50, L37, E3	N81, L12, E2	
Platelet count (x 10^3/mm^3)	**84**	**81**	**122**
Erythrocytic sedimentation Rate (mm/hour)	17		
MCV (FL)	**93**	**103**	**101.8**
Peripheral smear Macrocytic with eosinophilia			
Total Protein/ Albumin (g/dl)	**6.9/3.0 (May 2015)**	**6.17/2.23**	**6.6/2.4**
SGOT/SGPT(U/L)	**136/40 (May 2015)**	**64/36**	**72/43**
Total Bilirubin/ Direct Bilirubin (mg/dl)	**3.8/1.4 (May 2015)**	**6.86/2.86**	**5.99/2.28**
Alkaline phosphatase (U/L)	**110(May 2015)**	**531**	**484**
Direct coombs test-	Negative	-	-
Prothrombin time(sec)/ INR	31.5/2.62 (March 2016)	-	23.1/1.8
Creatinine (mg/dl)	0.5 (March 2016)	1.14	0.94
Sodium, Potassium (mmol/L)	-	133/ 5.1	134/3.9
Lipid Profile – Unremarkable	Urine Routine-Normal	Post prandial sugars - **265mg/dl (14.7 mmol/L)**	Random blood sugar >**400 mg/dl (> 22.2 mmol/L)**
HIV, Hepatitis B, Hepatitis C		Negative	

Table 2 Special Investigations

8AM, Serum Cortisol	**5.5** (5-23 mcg/dl)
ACTH (adreno-corticotropin)	16 (Normal)
Serum Ferritin	**1249** (20-250 ng/ml)
Iron	162 (65-175 mcg/dl)
Total Iron binding capacity	**183 (**250-450 mcg/dl)
Transferrin	128.1 (175-320 mcg/dl)
Alfa Foeto Protein	7.01 (<10ng/ml)
Vitamin B12	>2000 pg./ml
FSH	**0.879** (0.8-2.7 mcg/dl)
LH	**6.14**
Free testosterone	**3.6** (5.7-17.8 g/dl)
Bioavailable Testosterone	**58.1** (125.5-411.8 ng/dl)
Free androgen index	**14%** (35- 92.6%)
TSH	**0.647**
Free T 3 (2- 4.4)	**2.8**
Free T4 (0.8-2.7 mcg/dl)	**0.879**

Table 3 Imaging Investigations

Electrocardiogram	T inversion in Lead III, no AV block
Echocardiogram	Normal, no features of cardiomyopathy
Oesophago-gastroduodenoscopy (OGD)	Grade I, oesophageal varices with lax lower oesophageal sphincter (December 2016)
Ultrasound abdomen and pelvis	Features of chronic liver disease, minimal ascites
Computer Tomography (CT) of abdomen and pelvis	Features of chronic Liver disease with peri-portal, pancreatic and retroperitoneal collaterals, minimal fluid in pelvis.
MRI Brain - Normal	

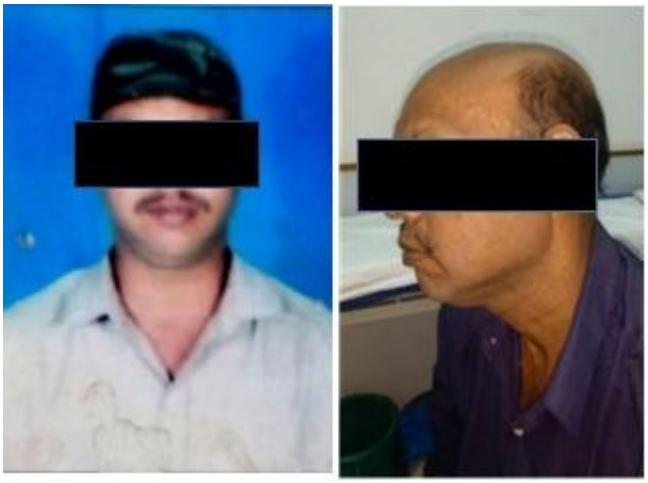

Fig. 1 Photograph of the patient taken 6 months prior to presentation in comparison to the present on the right showing diffuse skin hyperpigmentation

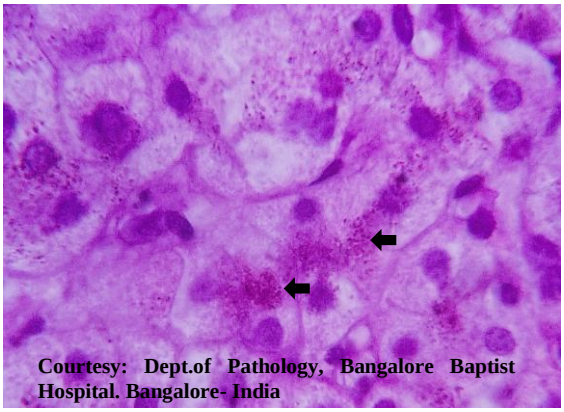

Fig. 2 Liver biopsy- Haematoxylin and Eosin stain showing, brownish iron pigments (black arrow)loss of architecture, thick fibrosis, inflamed bands

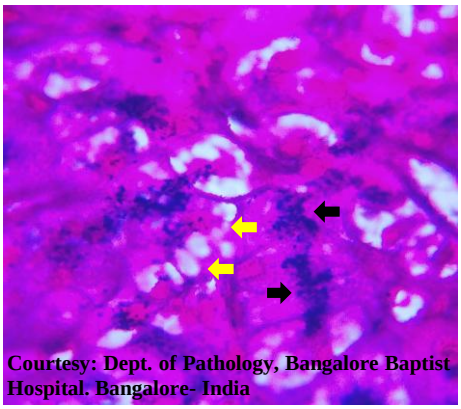

Fig.3 Liver Biopsy- Pearls Stain- showing brownish pigment (black arrow) with nodular hepatocyte clusters with vacuolated cytoplasm (Yellow arrow), and Focal ductal proliferation and focal cholestasis seen. Pearls stain- intracytoplasmic iron pigments in hepatocellular nodules (3+to 4+), features suggestive of cirrhosis of liver with increased iron

Discussion

Trousseau described the first case of Hereditary Haemochromatosis (HH) in 1865[1] HH is a Genetic disease resulting in systemic iron overload causing multi organ dysfunction. The most common organs involved are the liver, pancreas, gonads, heart and brain. If they are not detected early it can cause devastating injury to the respective organs. Our patient was being treated as alcohol related liver disease for the last 2 years even though patient was abstinent for 2 years, he had worsening liver function which was not evaluated. It is transmitted by autosomal recessive pattern. According to the Online Mendelian Inheritance in Man (OMIM)

database, hereditary haemochromatosis has been classified into 5 types based on the gene mutations. Type I implicated by the HFE gene, type II, sub classified as A, B, with the former due to hemojuvelin and the latter due to hepcidin genes. Type III has been related to transferrin receptor 2 and type IV due to SLC40A1 (Ferroportin) gene mutations. Type V has been reported in one family with mutation in FTH1 gene onchromosome 11q12 which is an autosomal dominant pattern[2] This was commonly reported among the people of Northern European origin. Two mutations have been identified. One is a substitution of cysteine for tyrosine at amino acid 282 (C282Y, nucleotide 845) and the substitution of histidine for aspartate at amino acid position 63 (H63D, nucleotide 187).

In a study done by Merry weather et al, more than 90% of haemochromatosis patients were homozygous for C282Y mutation. Worldwide allele frequencies were 1.9% for C282Y and8.1% for H63D, whereas it was10% in 90 Irish chromosomes for C282Y and 30.4% for H63D in chromosomes from Basque[3]. Another study by Robson et al, also showed that 91% (n=115) were positive for C282Y mutation and were homozygous[4] HLA-A3 and HLA-B14antigens were significantly higher. Among 51 patients with haemochromatosis who were studied in comparison with control group.

The occurrence of HLA-A3 was 78% vs 27 % in control; and HLA- B14 was 25 vs 3%. Thisstudy done by M Simon et al, shows that genetic haemochromatosis may be linked to histocompatibility genes[5] In a study done in North India, 215 individuals with beta thalassemia were screened for the mutations and only H63D was 9%, and C282Y was rare, and there was no correlation between increase in iron load and the present of the mutation in North India[6] Similarly another study which examined 59 unrelated healthy individuals from North India, 57 from South India and 75 thalassaemia major patients found that both mutations were rare in the populations and were higher among thalassaemia patients. Hepatic iron concentrations were higher in homozygous haemochromatosis, with iron concentrations of approximately 400µmoles/gm. This helps to distinguish early haemochromatosis from alcoholic siderosis[7]

However, in our patient hepatic iron was not weighted since the pearls stain showed 3 to 4+iron. Diagnosis can be made due to deranged liver function tests with multisystem abnormalities including elevated ferritin levels and our patient had transferrin saturation of 88.5 % and values greater than 50% are highly specific for Hemochromatosis; with elevated ferritin levels.

Other than HFE gene, hepatic expression of the gene for hepcidin (HAMP) was studied andwas found that lack of HAMP upregulation in HFE associated haemochromatosis despite significant iron load indicated that HFE plays an important part in iron overload[8] Transferrin Receptor 2 (TFR2) related HH occurs at an earlier age with multi-organ involvement. This is slower than the juvenile variety in which hemojuvelin mutation is implicated. When TFR2- HH is progressive complications include cirrhosis, hypogonadotropic hypogonadism and arthritis[9] Cardiomyopathy and diabetes are rare.

Hepatocellular carcinoma has not been described. In a study done in India among 5 patients with primary hemochromatosis which were diagnosed by clinical, biochemical and histological findings, lacked mutations in HFE, hepcidin and Ferroportin genes[10] Since the HFE mutations were negative in our patient, other mutations may be considered which includes transferrin receptor mutation 2, Ferroportin, hepcidin etc. however further mutation analysis were not sent due to financial constraints, which is a limitation of this study.

Conclusion

Unlike the western world, where health care is developed, India has a lack of facility for evaluating patients in the lower socio-economic strata owing to financial constraints. Hence cases are under diagnosed. Another factor being lack of awareness regarding the condition. Iron overload in South-Asians is probably non HFE type. However further genetic testing is required to categorise the genetic mutations.

Acknowledgement
The authors thank for the support received from Bangalore Baptist Hospital- Bangalore- India

Conflict of Interest: NIL

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List of Abbreviation

HFE- Official gene symbol for High Iron (Fe)
HFE gene CD28
BMI- Body Metabolic Index
Mg- Milligram
Mcg- Microgram
Ml- Milliliter
HH- Hereditary Haemochromatosis
OMIM- Online Mendelian Inheritance in Man database
HLA- Human Leukocyte Antigen
HAMP- hepatic expression of the gene for hepcidin
TFR2- Transferrin Receptor 2